Amendments to the Claims

The following Listing of the Claims will replace all prior versions and all prior listings the claims in the present application:

1. (Currently Amended) An oral pharmaceutical composition in the form of a tablet or a capsule for enhancing bioavailability and absorption of an active peptide agent comprising: an amidated active peptide agent, wherein the amidated active peptide agent ~~that~~ has been amidated such that an amide group has been added at ~~its~~ a C-terminus of an active peptide agent that~~, and~~ is not found in nature with an amide group at its C-terminus~~, said composition further comprising~~ and an absorption enhancer effective to promote bioavailability of said amidated active peptide agent, or a pharmaceutically acceptable pH-lowering agent that is present in said pharmaceutical composition in a quantity which, if said composition were added to ten milliliters of 0.1M aqueous sodium bicarbonate solution, would be sufficient to lower the pH of said solution to no higher than 5.5, wherein the composition enhances bioavailability and absorption of the amidated active peptide agent as compared with an oral pharmaceutical composition comprising the same active peptide agent having a free acid at its C-terminus instead of an amide group at its C-terminus.

2. (Previously Presented) The pharmaceutical composition of claim 1 comprising at least one pharmaceutically acceptable pH-lowering agent.

3. (Original) The pharmaceutical composition of claim 2 further comprising an acid resistant protective vehicle effective to transport said pharmaceutical composition through the stomach of a patient while preventing contact between said active peptide agent and stomach proteases.

4. (Canceled)

5. (Previously Presented) The pharmaceutical composition of claim 1, wherein said active peptide agent is prepared by converting a glycine-extended precursor to said active peptide agent.

6. (Previously Presented) The pharmaceutical composition of claim 1, wherein said active peptide agent comprises an amino acid that contains an amidated side chain.

7. (Canceled)

8. (Original) The pharmaceutical composition of claim 2, wherein said pH-lowering agent is present in a quantity which, if said composition were added to ten milliliters of 0.1M aqueous sodium bicarbonate solution, would be sufficient to lower the pH of said solution to no higher than 3.5.

9-10. (Canceled)

11. (Original) The pharmaceutical composition of claim 1, wherein said active peptide agent is linked to a membrane translocator which is capable of being at least partially cleaved in vivo by an enzyme.

12. (Original) The pharmaceutical composition of claim 3, wherein said protective vehicle is present at a weight which is no more than 30% of the weight of the remainder of said pharmaceutical composition.

13. (Original) The pharmaceutical composition of claim 3, wherein said protective vehicle is present at a weight which is no more than 20% of the weight of the remainder of said pharmaceutical composition.

14. (Original) The pharmaceutical composition of claim 3, wherein said protective vehicle is present at a weight which is between 10% and 20% of the weight of the remainder of said pharmaceutical composition.

15. (Original) The pharmaceutical composition of claim 3, wherein said protective vehicle is sufficient to prevent breakdown of said pharmaceutical composition in 0.1N HCl for at least two hours, yet permits complete release of all contents of said pharmaceutical composition within 45 minutes after pH is increased to 6.3 in a dissolution bath in which said composition is rotating at 100 revolutions per minute.

16. (Canceled)

17. (Previously Presented) The pharmaceutical composition of claim 1, comprising an absorption enhancer, wherein the absorption enhancer is a surface active agent.

18. (Original) The pharmaceutical composition of claim 17, wherein said surface active agent is absorbable or biodegradable.

19. (Original) The pharmaceutical composition of claim 17, wherein said surface active agent is selected from the group consisting of acylcarnitines, phospholipids and bile acids.

20. (Previously Presented) The pharmaceutical composition of claim 19, wherein said surface active agent is an acylcarnitine.

21. (Original) The pharmaceutical composition of claim 20, further including a sucrose ester.

22. (Previously Presented) The pharmaceutical composition of claim 1, comprising an absorption enhancer, wherein the absorption enhancer is a surface active agent selected from the group consisting of (i) an anionic agent that is a cholesterol derivative, (ii) a mixture of a negative charge neutralizer and an anionic surface active agent, (iii) non-ionic surface active agents, and (iv) cationic surface active agents.

23. (Previously Presented) The pharmaceutical composition of claim 1, comprising an absorption enhancer is selected from the group consisting of a cationic surfactant and an anionic surfactant that is a cholesterol derivative.

24. (Previously Presented) The pharmaceutical composition of claim 1, wherein said pharmaceutical composition includes at least two absorption enhancers, one of which is a cationic surface active agent, and another of which is an anionic surface active agent that is a cholesterol derivative.

25. (Original) The pharmaceutical composition of claim 24, wherein said anionic surface active agent is an acid-soluble bile acid.

26. (Previously Presented) The pharmaceutical composition of claim 1, further comprising an amount of a second peptide that is not physiologically active effective to enhance bioavailability of said peptide active agent.

27. (Original) The pharmaceutical composition of claim 3, further comprising a water soluble barrier that separates said pH-lowering agent from said protective vehicle.

28. (Original) The pharmaceutical composition of claim 2, wherein said composition includes at least one pH-lowering agent that has a pKa no higher than 4.2.

29. (Original) The pharmaceutical composition of claim 2, wherein at least one pH-lowering agent has a solubility in water of at least 30 grams per 100 milliliters of water at room temperature.

30. (Original) The pharmaceutical composition of claim 3, wherein all ingredients other than said protective vehicle are uniformly dispersed.

31. (Original) The pharmaceutical composition of claim 30, wherein said pharmaceutical composition comprises granules containing a pharmaceutical binder and, uniformly dispersed in said binder, said pH-lowering agent, said absorption enhancer and said peptide active agent.

32. (Previously Presented) The pharmaceutical composition of claim 1, comprising a pharmaceutically acceptable pH-lowering agent and an absorption enhancer wherein said composition is a solid dosage form wherein a weight ratio of said pH-lowering agent to said absorption enhancer is between 3:1 and 20:1.

33. (Previously Presented) The pharmaceutical composition of claim 1, comprising a pharmaceutically acceptable pH-lowering agent and an absorption enhancer wherein said composition is a solid dosage form wherein the weight ratio of said pH-lowering agent to said absorption enhancer is between 5:1 and 10:1.

34. (Original) The pharmaceutical composition of claim 2, wherein said pH-lowering agent is selected from the group consisting of citric acid, tartaric acid and an acid salt of an amino acid.

35. (Original) The pharmaceutical composition of claim 2, wherein said pH-lowering agent is present in an amount not less than 300 milligrams.

36. (Original) The pharmaceutical composition of claim 35, wherein said pH-lowering agent is present in an amount which is not less than 400 milligrams.

37. (Previously Presented) The pharmaceutical composition of claim 1, wherein said active peptide agent is human glucagon-like peptide 1, human glucagon-like peptide 2 or analog thereof.

38. (Canceled)

39. (Previously Presented) The pharmaceutical composition of claim 1, wherein said active peptide agent is insulin.

40. (Previously Presented) The pharmaceutical composition of claim 1, wherein said active peptide agent is human parathyroid hormone or analog thereof.

41. (Previously Presented) The pharmaceutical composition of claim 1, wherein said active peptide agent is a human parathyroid hormone analog having the first 31 amino acids of human parathyroid hormone wherein the 31St amino acid has the amide group.

42. (Previously Presented) The pharmaceutical composition of claim 1 wherein said active peptide agent is a human parathyroid hormone analog having the first 34 amino acids of human parathyroid hormone wherein the 34th amino acid is amidated at its C-terminus.

43. (Original) The pharmaceutical composition of claim 3, wherein said protective vehicle is a viscous protective syrup.

44. (Previously Presented) The pharmaceutical composition of claim 3, wherein a water soluble barrier separates said pH-lowering agent from said protective vehicle.

45. (Currently Amended) A method for ~~modifying a physiologically active peptide to increase its~~ enhancing oral bioavailability and absorption of a physiologically active peptide, while substantially maintaining its physiological activity, said method comprising:

amidating ~~a~~ the physiologically active peptide to create an amidated peptide having an amide group at its C-terminus, wherein the physiologically active peptide ~~that~~ is ~~not naturally amidated~~ found in nature with an amide group at its C-terminus ~~at said C-terminus~~; and

orally administering said amidated peptide in combination with (i) at least one absorption enhancer effective to promote bioavailability of said amidated peptide, or (ii) a pH-lowering agent that is present in said pharmaceutical composition in a quantity which, if said composition were added to ten milliliters of 0.1 M aqueous sodium bicarbonate solution, would be sufficient to lower the pH of said solution to no higher than 5.5.

wherein the bioavailability and absorption of the amidated peptide is enhanced as compared with the same active peptide having a free acid at its C-terminus instead of an amide group at its C-terminus.

46. (Previously Presented) The method of claim 45 comprising an absorption enhancer, wherein said amidated peptide and said absorption enhancer are selectively released together with at least one pH-lowering agent and/or protease inhibitor into a patient's intestine following passage of said peptide active agent, absorption enhancer, pH-lowering agent and/or protease inhibitor through said patient's mouth and stomach under protection of an acid resistant protective vehicle which substantially prevents contact between stomach proteases and said peptide agent.

47. (Canceled)

48. (Previously Presented) The method of claim 45, wherein said amidated peptide is prepared by converting a glycine-extended precursor to said amidated peptide.

49. (Previously Presented) The method of claim 45, wherein said amidated peptide further includes an amidated side chain.

50. (Previously Presented) The method of claim 45, wherein said pH-lowering agent and said absorption enhancer are both present.

51. (Previously Presented) The method of claim 45 comprising a pH-lowering agent, wherein said pH-lowering agent is present in a quantity which, if said composition were added to ten milliliters of 0.1 M aqueous sodium bicarbonate solution, would be sufficient to lower the pH of said solution to no higher than 3.5.

52. (Original) The method of claim 46, wherein said protease inhibitor is a stomach and/or intestine protease inhibitor.

53. (Original) The method of claim 46, wherein said protease inhibitor inhibits an enzyme selected from the group consisting of pepsin, trypsin, chymotrypsin, elastase, kallikrein and carboxypeptidase.

54. (Canceled)

55. (Previously Presented) The method of claim 45, wherein said physiologically active peptide is human glucagon-like peptide 1, human glucagon-like peptide 2, or an analog thereof.

56. (Canceled)

57. (Previously Presented) The method of claim 45, wherein said physiologically active peptide is insulin.

58. (Previously Presented) The method of claim 45, wherein said physiologically active peptide is human parathyroid hormone or an analog thereof.

59. (Previously Presented) The method of claim 45, wherein said amidated peptide is human parathyroid hormone analog PTH 1-31-NH_2.

60. (Previously Presented) The method of claim 45 wherein said amidated peptide is human parathyroid hormone analog PTH1-34-NH_2.

61-62. (Canceled)

63. (Previously Presented) The method of claim 45, wherein said increase in oral bioavailability is the result of enhanced intestinal absorption of the amidated peptide.

64-65. (Canceled)